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AD846556

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AUTHORITY

BDRL, ltr, 13 Sep 1971

AD846556

TRANSLATION NO. 247

DATE: July 1968

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Fort Detrick
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On fibrinous or hyaline degeneration in the tubercle and gumma.

by M. Vallat

Virchow's Archives, 89: 193-227 (1882).

For a number of years now, several investigators have noted a substance in various tissues and under the influence of diverse processes, which immediately attracted their attemtion by its peculiar appearance.

It consists of

1) a basic substance, and
2) a system of lacunae by which it is traversed.

The basic substance has easily recognizable physical properties. It is shiny, homogeneous, of glassy appearance and with strong light-refractive properties which apparantly increase upon hardening. Its edges are sharp. It therefore has a great similarity to amyloid substance, but does not glisten as strongly, and to waxy degeneration of muscle.

It seems to be partitioned into layers or bands of various forms and dimensions. At times small flakes of the size of erythrocytes are seen, or even smaller, at other times they are large, polyhedral, or one sees notched bands in net-like interconnection. Frequently all these forms are found simultaneously, in all stages of transition.

The fissures characteristic of this substance, as they are found almost invariably, are limited directly by the substance and have no special wall. If they are relatively sparse, they assume the form of quite uniform canals and show net-like anastomosis. The more the basic substance is divided into smaller fragments, the more indistinct are the canals. Sometimes they form star-shaped gaps. The canals nearly always show nuclei, usually contracted or rod-like, but always strongly impregnable with stains. This is the most constant element. In addition, whole cells or granular masses are found in certain cases. The basic substance fluctuates somewhat in its response to staining agents. Now and then it stains quite intensely and uniformly with carmine or hematoxylin; in other cases it resists their effect. This depends primarily on the length of time it is exposed to the dyes. It may suddenly stain intensely, from one moment to the next. It absorbs carmine more readily than hematoxylin. -- Iodine has no effect. -- At times methyl violet produces a light pink coloration, but far less so than in the case of amyloid. -- Dahlin, gentian produce pink if the substance is well developed, while the nuclei of the remaining tissue turn violet. However, this stain is unable to reveal the initial stages of degeneration. -- Magdala and safranine cause a dark purple color. -- Picrocarmine of Ranvier gave the same results as other carmine tinctions (alum or borax carmine). I have also tested the modification recommended

by Neumann for the picrocarmine stain: Partial decoloration with hydrochloric acid, in order to permit more distinct differentiation of picrin (1). The analog led me to expect a yellow coloration, but I failed to observe a difference compared to ordinary picrocarmine staining.

According to its chemical reactions, this substance belongs to the albuminates. It is bleached, but not dissolved, by mineral acids and acetic acid.

This substance is first mentioned by Schueppel (2), who describes a metamorphosis of the epithelioid cells and the stroma of the tubercle in tuberculous lymph glands, designated by him as cornification (homogeneization of the epithelioid cells with loss of the nucleus, strong luster and ultimate fusion, possibly also with the reticulum). His description establishes positively that the formation of the same substance is involved. It seems remarkable that he has seen it only once among 40 cases of tuberculosis. Yet he also describes changes of the stroma, which very probably belong to the same process ("thickening of the trabeculae of the adenoid network into wide, wholly homogeneous, strongly lustrous bands, etc.,--- striking similarity to certain forms of the diphtheritic reticulum." Page 47).

Grancher's (3) observations also belong in this category, as the following will show, although P. Meyer disagrees. Grancher finds a colloidal or glassy transformation of the cells in caseous pulmonary foci, which first swell, then become homogeneous and form a compact mass prior to caseation.

The first, more precise description of this tissue is found in Langhans (4). He found a tissue on the placental side of the chorion which had a homogeneous, strongly lustrous and light-refractive basic substance, traversed by numerous canals of varying caliber, which surround granules and especially free nuclei at regular intervals. He attributes it partly to the parental blood in the intervillous blood spaces, partly to a peculiar, large-cell layer on the chorion, which he has also discovered recently (5) in the earliest stages of ovarian development and which he considers a part of the serous envelope. He concluded of both bases that this tissue is formed by fusion, partly of red and white blood cells, partly of those large cells in conjunction with a small amount of intercellular substance, and that the canals are created secondarily and originate with the nuclei. He even suggests the possibility of growth by intussusception and ascribes to it a certain organization, though incomplete.

Since it is directly related to ordinary reticular fibrin coagulates and, at least partly, precipitates from the blood, he calls it canalized fibrin.

In addition to this form, he describes another in which the canals and fissures are more numerous and relatively wider, and the particles of basic substance assume the form of small spherules (globular form).

According to his data, the same substance is found in phlebolites, in the white thrombi (6) that develop in arterial wounds, also in the diphtheritic network and in tubercles, where he found it in the periphery of caseous masses in the spleen.

Cornil has also seen this mass. In the second edition of the Manuel d'histologie pathologique by Cornil and Ranvier (I. p. 654.1881) we find the following description: "The tuberculous and inflamed ganglia show, in their cortical substance, in the center of the follicular tissue, small colloidal islets; they consist of a mass of lymphatic cells two or three times larger than normal, clear, transparent, without nuclei, containing colloid. These cells stain pink with picrocarminate of ammonia. They do not give a single reaction associated with amyloid."

The most numerous investigations have their origin in v. Recklinghausen's laboratory.

v. Recklinghausen has called these and similar substances hyaline. According to the abstract (unfortunately all too short) of his report to the 52. meeting of German naturalists and physicians at Baden-Baden (7), hyaline represents a normal component of cellular protoplasm and separates from it in the form of droplets, especially during necrosis; he was able to produce it synthetically by increasing the concentration of tissue fluids (dehydration, salt solutions) in the blood; he finds it in post mortal coagula, particularly of the hepatic vein, but also under different conditions developing in life. He includes here Langhans' canalized fibrin, degeneration of the wall of the small renal arteries in acute nephritis, hyaline in the wall of aneurysms, as described in detail by P. Meyer, and in the intima of vascular walls, diphtheritic exudate, and especially the vascular changes connected with it. According to P. Mayer, v. Recklinghausen has also found it in thyreoideal cysts, in hematocele, in certain infarcts and in tubercles. He recalls the similarity of this substance to amyloid and surmises that even cuticular formations and intercellular substances are attributable to hyaline. It is said to take the form of canalized fibrin only in locations where it is subjected to pressure. Only P. Meyer, his assistant, has expressed an opinion on the manner in which these canals develop.

Of Recklinghausen's followers, Wieger (8) was the first to continue research into degeneration of lymph glands. He first describes a form which is associated exclusively with blood vessels; their walls, especially the adventitia, are enormously thickened and transformed into a wholly homogeneous, shiny mass, which he attributes to aggregation and fusion of white blood cells. The process is said to frequently terminate in calcification.

In the second part of his discourse he reports on 2 cases of degeneration of the lymph-glandular tissue proper. It takes, in its developed stage, the form of aggregations which Wieger divides into two zones. The peripheral zone consists of small hyaline lumps, partitioned by cracks and fissure-like gaps, in which denuded nuclei are found in varying amounts. These small lumps are said to fuse and from a

homogeneous, transparent substance which in turn divides into oval or obtuse-angled clods. They are contained in the strongly enlarged meshes of the reticulum, which reveals a striking preponderance of cells. Wieger describes the hyaline substance as emanating from the cellular protoplasm.

Paul Meyer (9) has studied the hyaline material in the walls of aneurysms of pulmonary arteries in connection with tuberculous cavities; it occurs here with the aspect of canalized fibrin, it forms the wall of the aneurysmal enlargement and changes directly to thrombotic deposits on the inner surface. According to his data, the substance in the deteriorating wall is composed of white blood cells, possibly even of elements of the intima proper. In order to explain the genesis of canals, Meyer compares hyaline with semi-solid fat which contains vacuoles filled with a serous fluid. This liquid does not mix with the main mass. In the presence of uniform pressure (in particular, arterial pressure) the liquid is distributed uniformly throughout, and thus a system of more or less regular canals is formed instead of polymorphous lacunae. He deems it probable that the infiltration of white blood cells also has a part in the formation of canals.

Opinions expressed by Langhans concerning this substance cause me to mention Neumann's paper (10); according to Langhans, fibrin is present here in a special modification, changing directly to common reticular fibrin, however. Accordingly, in the case of tubercles, there would be a fibrinous metamorphosis of their tissue, a position that has great merit since the tubercle may be considered to be a specific inflammation. Neumann supports the earlier opinion concerning the involvement of the connective tissue in the formation of the fibrinous pseudo-membranes of the serous layers, as interpreted chiefly by Buhl; he speaks of its fibrinoid degeneration. In addition, he describes such changes of the connective tissue in the vascular intima in the case of aneurysmal enlargements and arteriosclerosis; in synovial membranes (formation of corpuscula oryzoidea); in the mucous membranes in diphtheria.

Recently Peters (11) has described hyaline degeneration in diphtheria of the air passages. He adds to the observations made earlier by v. Recklinghausen concerning the changes in the blood vessels connected therewith. These affect the capillaries and small arteries. At times their lumen is filled by a hyaline thrombus, at times their wall itself is degenerated, and this in the media (possibly in the adventitia, also). These two forms also occur simultaneously. If the disease was short-lived, only the vessels are involved; if of longer duration, hyaline deposits are found also in their immediate proximity. Peters further investigated the diphtheritic pseudo-membranes from this point of view. He differentiates a special form, the deposit, by the designation hyaline membrane. According to him, it emanates from diverse elements: 1) from epithelial cells, 2) from connective tissue cells, 3) from the elements of the vascular wall and white blood cells, 4) from pus cells, no matter of what origin. Degeneration takes the following course. First the epithelium changes, then the contents of the blood and lymph vessels, then hyaline of the vascular wall is formed, and finally the neighboring

parenchyma also degenerates. Hyaline is present more frequently in light cases, rather than ulcerative cases, and he therefore attributes to it a protective influence against invasion by the poison.

These observations are supported by a remark by Baumgarten (12), who has rather frequently seen Neumann's fibrinous degeneration in tuberculous inflammation of cerebral vessels.

Arnold (13) mentions the presence of hyaline in tubercles of the lymph glands, where he found them in 38 out of 90 cases, agreeing in the main with Wieger. He also saw it in splenic tubercles. He fails to mention it in descriptions of tuberculosis of the kidney and liver.

This historical summary tends to lead to the conclusion that the substance under consideration is not a mere pathological curiosity but is met rather frequently in different pathological processes; it is found even in normal organs, as the placenta, so that its significance cannot be inconsiderable.

We find it primarily in the following locales:

1) in the normal placenta,
2) in vessels (thrombi, aneurysms, atheromas),
3) in various inflammatory new formations (diphtheria, etc.),
4) in tubercles and, as I shall add,
5) in gumma.

At this time a limiting remark is appropriate. Since we do not know of a [illegible]tive chemical reaction for this substance, as we do for amyloid, [illegible]ossible at this time to prove that all of the above descripti[illegible] always dealing with the same material. For example, one could ask whether all changes of the vascular walls called hyaline degeneration really represent this process. Thus I have in some cases found the walls of the small arteries changed into a substance which wholly resembles canalized fibrin. In other cases, however, the media was transformed into a uniform, homogeneous mass, refusing to absorb stains of any kind. This question cannot be answered at this time.

A decision concerning the question whether this substance is attributable to fibrin with Langhans, or whether it is to be given a special position with Recklinghausen under the designation of hyaline, is possible only on the basis of investigations relating to all objects listed by these two researchers. I do not intend to do this in the following, since I have only dealt with its occurrence in the tubercle and gumma, and I shall refer to the two investigators side by side, without preference.

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I have examined tubercles of the spleen, liver, kidney, lung, lymph glands, adrenal glands, the central nervous system and the serous membranes.

Of all these organs, I have found hyaline degeneration to be most constant and in its most characteristic forms in the spleen; I was able to establish its presence here in about one-half of all cases.

If hyaline is present in large amounts, it may be recognized with the unaided eye. As a rule, caseous degeneration is found at the same time. The opaque, caseous parts are surrounded by a fairly wide, glistening zone, by a light brown color (after hardening in potassium chromate and alcohol). This is the questionable canalized fibrin. In some cases there is, on the outside, a highly transparent, grey zone; this represents an aggregation of cells.

These 3 zones are located in the level of the remaining sectional surface or, as a rule, are prominent. If the tubercles are still miliary and transparent, if the canalized fibrin in contained therein in but small amounts, these tubercles do not differ macroscopically from others. The distribution of fibrin in the tuberculous spleen is varied; usually it is very copious, so that one meets it on nearly every microscopic section. In other cases it was found in a small number of tubercles only.

Let us now proceed to its description and examine its relation both to the elements of the tubercle and the splenic tissue proper.

One finds many varieties in this connection. In a certain number of cases there are miliary or somewhat larger, fused tubercles, sharply delineated from the normal surrounding tissue, some of them consisting of hyaline substance. Here the hyaline degeneration seems to occur at the expense of the tubercle's elements and seemingly has no direct connection with the lymphatic tissue of the spleen.

In contrast thereto, other cases show the canalized fibrin as being interspersed in the splenic tissue in a more diffuse manner, where it gradually fuses with the normal environment. Here there are no sharply delineated tubercles.

Let us first examine the former variety.

As already mentioned, we are dealing here with very small, miliary or fusing tubercles which, however, are sharply demarcated in all cases. Canalized fibrin appears here almost as soon as the tubercle starts forming. The various stages may usually be studied in the same organ. In the first stage of the tubercle, a simple aggregation of lymphatic cells is seen at certain points between the lymphatic tissue, easily recognized after staining. The cells are more closely together, there are more stained elements in the same space, the color of the stain therefore appears more saturated. Arnold (loc. cit.) has proved that such commencing tubercles are generally found in the follicles.

In slightly more advanced foci the center is formed by variously shaped epithelioid cells with one or more nuclei; very frequently giant cells with peripherally situated nuclei are seen. The periphery is

always formed by small, round cells which limit the tubercle. The center is light yellow owing to the finely granulated protoplasm of the epithelioid cells.

There is no noteworthy intermediate substance between the epithelioid cells, while a reticulum is present between the round cells of the periphery, as is true of the neighboring splenic tissue. These tubercles are completely developed, with all of their characteristic elements, but still of very small dimensions. In this period the canalized fibrin begins to form, always in the center of the tubercle. Small, shiny clods are seen here, very densely packed. The larger the tubercle, the more this substance gains in extent, until it represents the major part of the nodule. Now the oldest, i.e. the central parts of the canalized fibrin takes on a slightly different character. Here one sees larger, lustrous, polyhedral clods which delineate small canals with their sharp edges. The canals form a network, the size of the mesh depending on the size of the hyaline lump. These lumps are always largest at the center. They get smaller toward the periphery and ultimately dissolve into an accumulation of small lumps, as mentioned above. The canals become less distinct in the process. In the interior of these canals there are nuclei, usually contracted or rod-shaped, in changing numbers, but generally more numerous at the periphery than at the center.

At the periphery of this central hyaline mass there are also ordinary epithelioid cells and one or more giant cells, the latter at times surrounded half-way by the substance. Almost invariably their nucleus is located on the side which is opposite to the canalized fibrin.

The tubercle, changed in this manner, is always distinctly delineated from normal tissue by the small-cell zone. The cellular zones and the fibrin are somewhat opposite in their development, however: If the fibrin is strongly represented, as in larger tubercles, the zones are extraordinarily thin.

I have never seen blood vessels in this type of tubercle.

An additional metamorphosis, taking place upon gradual enlargement of the tubercle, is represented by caseation. It always starts at the center of the canalized mass and advances toward the periphery, but is invariably surrounded by a zone of canalized fibrin, with which the caseum meets in imperceptible fusion. We shall return later to the composition of the caseous mass.

How does the canalized fibrin form in these cases? I cannot give a positive answer to this question. At any rate, its place was formerly occupied by tubercular tissue with its epithelioid and giant cells. It is possible that the epithelioid cells themselves change directly into this mass, but I have not been fortunate enough to observe a cellular metamorphosis, as described by Schueppel, Wieger and Arnold in connection with lymph glands. According to these authors, the epithelioid cells become hyaline, swell, and lose their nuclei. One fact that seems to speak against such a direct metamorphosis of the epithelioid cells to

hyaline masses in the present variety of tubercle, is the circumstance that the small hyaline clods, at the periphery of the canalized substance, are much smaller than the epithelioid cells in close proximity. One would have to assume that each of the epithelioid cells divides into a large number of hyaline lumps during the transformation.

But how are the canals formed? What is the origin of the nuclei contained in them? Perhaps the same process takes place which Langhans assumes for the canalized fibrin of the placenta: Fusion of cells and secondary development of canals from the site of enclosed nuclei. This would explain the peculiar forms of this substance. Unfortunately I have not found any clues in that direction. Perhaps the canals are formed by a stream of nutritive fluid or an infiltration of white blood cells?

Since the hyaline substance invariably consists of small clods at its periphery, the small lumps must merge again during the formation of completely developed fibrin, with its regular canals. — Or, assuming that they unite in a network, the presence of the central, canalized fibrin with its large clods could be explained by the swelling of its trabeculae; the canals would expand further and the greater distances between nuclei in the center could thus be clarified. Does growth take place by intussusception, as assumed by Langhans in the case of placental canalized fibrin? Obviously a number of highly interesting problems require solution. I must be content with merely pointing them out. At any rate, there should not be a particularly high pressure here, assumed by v. Recklinghausen and Meyer to be a preliminary condition for the formation of canals, no more than in the large intervillous blood spaces of the placenta.

The nuclei always stain easily. Frequently they are somewhat shrunken or narrow, rod-shaped, as if they had been exposed to a certain amount of pressure.

Since almost no intercellular substance is found between the epithelioid cells in this type of tubercle, I cannot report anything on its nature.

I have another variety to add to this first type of tubercle with hyaline degeneration. The tubercles of this type usually are rounded, sometimes slightly rectangular; they consist of the following concentric zones from the periphery to the center. First a zone of densely packed round cells which sharply demarcates the whole focus from the splenic tissue; then a fibrous zone with fibroid layers running parallel to the periphery. Between the layers there are fusiform cells with a large, oblong nucleus. The inner border of this zone usually is sharp, and is followed by canalized fibrin, which fills out the entire center if the tubercle is still small. If, on the other hand, it is large, the canalized fibrin itself forms a circular zone of various width, which gradually fuses with the central caseum. The first two zones, the round-cell and fibrous layers, are always less developed than the central mass, which they encapsulate. Almost as a rule, there are one

or more giant cells in the fibrous zone, most frequently in its center, at times at the inner border, touching the hyaline substance. Now and then giant cells are found also in the round-cell zone.

The canalized fibrin takes the usual form here, with the exception that the canals favor a radial arrangement, most distinctly seen at low magnification. In this case the canalized fibrin does not border on small hyaline clumps on the outside, but delineates rather abruptly against the fibrous zone. By the use of very thin sections I have, on numerous occasions, observed that the bands of hyaline substance pass directly into the layers of fibrous tissue. The latter takes on a homogeneous character in this connection. The differences between the two substances are due primarily to luster, transparency and staining qualities, as hyaline stains diffusely and intensely, the fibrous substance not at all. In this case a direct transformation of the fibrous tissue into the hyaline substance suggests itself. The caseous mass is opaque. In order to complete this picture, I must add that I have often seen an obliterated vessel in the center of the caseum. As a rule this vessel was closely surrounded by a mass which had the optical characteristics of hyaline, but contained no canals. — Upon careful staining with a nuclear agent, e.g. Grenacher's borocarmine, the various zones are vividly contrasted. The round-cell zone is characterized by densely packed, dark red nuclei; the fibrous zone is colorless, with isolated nuclei; the fibrin is stained diffusely and intensely, the caseum is colorless or light yellow.

We are dealing here with a special type of tubercle, as I have always found the same characteristics, the same elements in consistent arrangement in all tubercles of the same organ, and this in several cases of splenic tuberculosis.

As evident from this description, we are presented here with the picture of the fibrous tubercle, as described by Langhans and Schueppel, with the addition of a hyaline substance interpolated between the fibrous zone and the caseous center.

I have, on several occasions, observed the initial stages of the tubercle prior to the development of connective tissue and fibrin. I found an aggregation of epithelioid cells surrounded by a tissue of round and fusiform cells enclosed in a net of connective tissue; there were round cells more toward the periphery. It appears, therefore, as if the canalized fibrin takes the place of the epithelioid cells and, by its increase in volume, compresses the peripheral zone, primarily at the expense of the cells, so that the basic substance predominates.

In both of the described tubercles, fibrin is found only within the tubercle and has no direct connection with normal splenic tissue. However, foci of canalized fibrin may also be found in a third series of cases, where it is directly interspersed in the splenic tissue. Here the hyaline masses gradually fuse with normal tissue. Often giant cells are the only sign of a tubercle. (Incidentally, tubercles were invariably found also in other organs in these cases).

As a standard of this last form, I shall describe a case which, owing to its consistency, enabled me to obtain the thinnest sections with the aid of the large Thoma microtome. I have also found the same in other cases, however. The nodule is relatively large, up to 2 mm in diameter. The weak magnification shows almost no trace of normal tissue; instead, isolated, irregularly shaped foci of a shiny, homogeneous substance are seen, with a network of lines suggesting canals. In somewhat thicker, unstained sections the color is yellowish. It either reacts negatively to stains, or stains diffusely and intensely, depending on the duration of treatment.

The foci are contrasted against the surroundings by their lustre. They are surrounded by tissue in which a few stained nuclei and fibrillar, colorless tissue can be recognized. There follows a zone toward the periphery in which the cells are somewhat more densely packed than in the normal, bordering lymph tissue, which gradually takes up this zone. Here giant cells are found in abundance. Thus there are three zones, sharply demarcated by their color. —— The number, shape and size of these foci within a nodule are quite variable. In some cases the nodule consists of a large, centrally located shiny mass, and the two other zones, the one with copious cells and the one poor in cells, are found only at the periphery, toward the normal splenic tissue. If, on the other hand, the foci are smaller and more numerous, as is usually the case, the peripheral zones naturally fuse together and traverse the sectional surface of the node irregularly in the form of cellular bands, containing giant cells.

Under high magnification the larger, homogeneous foci seem to consist of hyaline, angular clods with rounded contours and sharp borders (at least in places where the section is not very thin), of the size of liver cells, which are bordered by thin canals anastomosing in all directions. The tissue takes on a reticular appearance thereby. The higher the grade of hyaline degeneration, the more regular are the course and caliber of the canals. In typical cases their lumen is identical nearly everywhere and they anastomose almost regularly at a right angle, recalling biliary capillaries. As in the latter, cross sections of canals rising from the depths are seen at the junctions. In this developed condition, the canals appear nearly empty, they contain only isolated deformed nuclei, elongated to rods which, however, stain as intensely as normal nuclei, or some granular detritus. The hyaline substance is not uniformly homogeneous as, for instance, is urinary cast, but somewhat irregularly shaded. Very thin sections present a slightly different picture. One no longer has the impression of isolated plaques with interpolated canals, but the substance appears in the form of branched bands with irregular, jagged borders which give them a gnarled appearance. At times there seem to be trunks with ramified branches on each side. The picture of arabesques is presented, as if cut into the mass of basic substance, since all these lines are joined, and independent lumps cannot be seen anywhere. The spaces between them are canals, which do not have as regular a form now. As already revealed by the shape of the canals, there are no independent clods; even the basic substance forms a net, as do the canals; the size

of the junctions and trabeculae or connective parts are different, however. While the junctions of the canalicular network are small, the connective pieces thin and long, the basic substance has very short and wide connecting pieces and very large junctions which give the impression of clods, especially with low magnification and slightly thicker sections. The connection between these clods is frequently found in a deeper layer, as revealed by high magnification.

This description refers only to the central portion of the shiny mass; toward the periphery it again seems to divide into numerous smaller lumps and bands, with spaces of various form and size between them, still having the aspect of canals. This part as a rule forms only a narrow border zone around the main mass, with which it has common optical and staining properties. The nuclei are somewhat more numerous in the canals. Very thin sections tend to show that this part also consists of ramified trabeculae of a hyaline substance, albeit finer. Here, too, the smaller clods only represent the junctions or the optical cross-sections of the trabeculae. This zone, apparently consisting of small lumps, fuses toward the periphery with a fibrillous, light tissue with few nuclei. As seen under high magnification, it consists of a reticulum with thick trabeculaw and especially of thick junctions with a denuded nucleus, a round cell, or some granular detritus in the narrow mesh. At times the meshes contain a certain amount of finely granular, round bodies of the size and shape of neighboring cell nuclei, but without their staining qualities. Perhaps a destruction of cells by pressure is involved. The trabeculae themselves are light, very finely granular, often shiny in the center, homogeneous, but failing to react to stains; now and then, particularly at the junctions, they contain nuclei. This reticulum is most developed in the proximity of canalized fibrin, cells and nuclei are sparse and isolated; they increase toward the periphery, the trabeculae become thinner and finally the tissue is distinguished from normal splenic tissue only by its slightly increased thickness and transparency, as well as by the homogeneous nature of the reticulum. There is no sharp borderline between the two tissues. The preceding forces to the conclusion that the canalized fibrin represents only the considerably thickened and homogeneated reticulum of the lymphatic tissue.

In detail, the transformation would occur as follows: First, slight thickening of the reticulum with increased transparency; thickening advances, while a certain number of cells disappear (perhaps due to pressure). The remaining cells lose their protoplasm (which perhaps contributes to the thickening of the trabeculae, divorcing itself from the nucleus). Part of the trabeculae may fuse; at any rate they become thicker, the homogeneous appearance and lustre increase, the meshes are compressed to canals with regular courses and now contain sparse, shrivelled or rod-shaped nuclei at longer distances.

In order to complete the description, I must discuss the connection between giant cells and fibrin, and the changes in the blood vessels.

Giant cells occur in great numbers, at times they are situated at the periphery of the fibrin, in which case (as already mentioned) their nuclei are located at the side averted from fibrin; their protoplasm seems to fuse directly with the basic substance of the fibrin; it is true that high magnification reveals a sharp and distinct border, but the latter follows a very jagged line; fibrin as well as cellular protoplasm interlace with their serrations and create the impression as if the giant cells were defective, i.e. as if a part of their mass had been transformed into fibrin. One also finds giant cells with well-preserved nuclei among the fibrin; in some cases there are figures in the fibrin that resemble giant cells in form, size and granular appearance, except that nuclei cannot be found in them, not even by means of the best stains.

Normally no trace of vessels is found in the fibrinous masses, but sometimes an artery with a large caliber ($\frac{1}{2}$ mm or more in diameter) forms the center of a small nodule of fibrin. The lumen is narrowed or almost completely closed by the thickening of the intima, rich in cells; media and adventitia are changed to completely developed fibrin. The nucleated canals of various widths traverse the wall cross-wise or more obliquely, at times they form a delicate net with oblong meshes parallel to the intima; they are connected firectly to the surrounding canals. At some points they are sparser and may even be absent at narrow points in the circumference.

I have observed a similar change in the media of smaller arteries, but the mass has less lustre and contains no canals. In place of the intima, i.e. on the inner surface of the elastic layer, there is a mass of similar appearance, delineated in a wavy line toward the interior. On this edge there are some nuclei, probably those of the endothelium. The lumen is severely narrowed. These small arteries are located in nearly normal tissues. I should like to stress in this connection that reagents for amyloid have had a wholly negative result here.

We see thus that the process taking place in the formation of canalized fibrin has a close resemblance to that described by Koester and Eberth in connection with amyloid degeneration of lymphatic tissue. According to these investigators, it proceeds from the reticulum, the trabeculae of which become thick, homogeneous and shiny, while the round cells are not participants but succumb to pressure. I have established that the reticulum thickened during amyloid degeneration of the spleen is wholly identical with the reticulum of the first stage of fibrinous degeneration. At times sago spleen, the completely developed amyloid substance, reveals a network of lacunae which almost completely resemble the canals of our degeneration. Perhaps there exist other connections between these two types of degeneration, hyaline and amyloid. One could point out that both are connected with the blood circulation, since the canalized fibrin as well as amyloid is found preferably on the vascular system (arteries) and most frequently in organs rich in blood. The analog is thereby exhausted, however, and we must for the time being forego the ennumeration of additional connecting characteristics.

I have several times found both types of degeneration in the same organ. They appear closely together without, however, entering into connection. Thus an amyloid follicle is seen and in close proximity a tubercular nodule in which the fibrin has the same structure. The two substances cannot be considered identical, since the staining reagents of amyloid have no effect on our substance; this is true especially of iodine. In certain cases methyl violet can elicite a light pink coloration, but it cannot be compared to amyloid in the intensity of its color; it disappears more rapidly, within 24 hours on glycerol preparations, while I possess amyloid preparations treated in the same manner which show unchanged color intensity for over a year. On the other hand, it is possible to distinguish the two substances without this reaction. Amyloid has a stronger lustre, while fibrin is somewhat duller, the latter also has a more yellowish tone. Recently Raehlmann (14) has published several cases of localized hyaline and amyloid degeneration of the conjunctiva in the form of tumors in which he claims to have seen a closer transition from one to the other.

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The tissue which is closest to that of the spleen, and the tubercles of which show hyaline degeneration nearly as frequently, is that of the lymph glands. As this has been described by several investigators, I shall not treat the details and shall only point out a few peculiarities.

First I must mention that I have not found the canalized fibrin to be as extensive as in the spleen. The foci were slightly smaller and did not contain such a regularly developed system of canals. Fibrous degeneration plays a far more important part in the lymph glands than in the spleen. Thus very ordinary foci of canalized fibrin are found to be separated by wide spaces, the latter being filled with a connective tissue poor in cells, resembling scar tissue. On the other hand, I have never seen the fibrous type of tubercle with a hyaline zone.

I believe I saw the direct transformation of epithelioid cells to hyaline, as described by Wieger, i.e. at the periphery of a focus of canalized fibrin, next to epithelioid cells, bodies of the same form and size as the latter, but entirely hyaline and without nuclei. In this case the canalized fibrin did not divide into small lumps at the periphery.

As in the spleen, I noted a few small vessels with completely hyaline walls in the center of the foci.

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After the spleen and lymph glands, I found our degeneration most frequently in the liver, even if considerably less often than in the other two organs.

It is found here in the first stage of tubercles or in later stadia in conjunction with casecus degeneration.

I shall describe a case of tuberculosis in the first stages. — The tubercles are situated in the periphery of the acini, as often found in the arteries and bile ducts, in Glisson's sheath. They are rather uniformly round, isolated or in small groups. The center consists of canalized fibrin, the light periphery of the usual lymphatic bodies and epithelioid cells; in addition, fusiform cells are found. These elements are relatively few in number, there are considerable amounts of connective tissue between them which, as I have often observed, has a reticular arrangement. The trabeculae are finely stratified. This connective tissue is as richly developed in the youngest and smallest tubercles, without a hyaline center.

Closer to the centrally located canalized fibrin there are very small glistening granules which seem to be situated on the trabeculaw of this connective tissue network. Initially they are few in number and do not cover the trabeculae. The closer one gets to the center, the more they gain in number and size, until they touch; at the same time the protoplasm of the cells located in the meshes disappears and only the nuclei remain. Part of them are completely dilapidated and I have found granular bodies here, as in the spleen, which resemble nuclei but did not stain. Toward the center the small shiny bodies fuse, the meshes of the net are compressed to canals and result in fully developed canalized fibrin. The process therefore is identical with the one observed in the spleen.

Giant cells were copious in this case, most of them located in the peripheral zone, some at the edge of canalized fibrin. Again they had no nuclei on the side closest to fibrin, and their protoplasm fused with the fibrin. At times I found a giant cell in its midst, with distinct or indistinct contours and well-preserved nuclei.

In addition, the periphery contained arteries as well as small and larger bile ducts. The arteries were passable and showed no hyaline degeneration. The bile ducts sometimes contained a solid yellow mass (bile) and in these cases the fibrin was also colored a uniformly intense yellow. Fresh sections made with the ether microtome retained the color only for a few days in glycerol, disappearing thereafter.

The smaller bile ducts, at times found in large numbers in the periphery, are analogous to those described by Arnold in connection with hepatic tubercles and must be considered as newly formed. The fibrin itself contained no traces of small or larger ducts.

In other cases the connective tissue is even more developed; in that case the acinous peripheries reveal large foci consisting of a reticulum with very thick trabeculae; each mesh encloses a round cell or a granular mass. The cellular nuclei give a weak staining reaction. In certain cases the reticulum seems to be absent and in its place there is either a group of epithelioid and giant cells in the form of a small nodule, or a large focus of canalized fibrin of the same size. The fibrinous foci are often in close proximity, then the fibrous reticulum located between them itself succumbs to hyaline degeneration. It is

easily established that the connective tissue as well as the cells may change into hyaline substance, since the confluent fibrinous foci distinctly show parts that originally belonged to the aggregation of cells and those belonging to the reticulum; each of them has retained its particular form. The reticulum is also recognizable, but its trabeculae have become hyaline and its cells have disappeared. Similarly, hyaline masses with a round shape are seen nearby, possessing elements of the exact form and size of epithelioid cells.

As in the preceding case, there are giant cells, newly formed bile ducts and unchanged arteries in the reticulum.

Finally I have found canalized fibrin in caseous tubercles, and here almost invariably forms that resembled the splenic tubercles described above. There are large, caseous foci, surrounded by an envelope of fibrous tissue, only the peripheral zone of round cells is missing. In its outer layers, the fibrous tissue consists of concentric strata and fibers with interspersed fusiform cells and giant cells. In the direction of the caseous mass, the fibrous tissue becomes homogeneous and, due to the appearance of transverse fissures, assumes the form of clods, with free nuclei between them. The connective tissue seems to fuse directly with the hyaline masses that form a narrower zone around the caseous center. In the middle of the caseous mass, a focus of fibrin is frequently found, with an artery at its center, the wall of which is completely changed to canalized fibrin. In the close proximity of the artery, the hyaline mass also has regular canals, but they become indistinct at greater distances and disappear completely. The fibrin then fuses gradually with the caseous mass in the form of irregular, jagged bands. There were few nuclei in the fibrin.

The factor that is particularly conspicuous in hepatic tubercles with hyaline degeneration is the strong development of their connective tissue. In its initial stages the process resembles interstitial hepatitis. In addition, the connective tissue contributes directly to the formation of the hyaline substance.

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Degeneration in the kidneys is far less frequent than in the liver. I have seen it only once or twice among 20 cases, while the ratio for the liver is about 5:20. I have never found it in miliary tubercles, but always in conjunction with caseation. As a rule the process is seen as follows. In the center of a more or less caseous focus there is an artery, usually of considerable caliber (a few tenths of a millimeter). Its wall, at least the media and adventitia, is changed to a well-developed canalized mass or is completely homogeneous. The lumen at times contains hyaline lumps adhering to the wall, sometimes it is closed by intimal proliferation or reveals only a granular mass with a few nuclei, or the lumen is entirely empty. In the surroundings of this artery there is a zone of hyaline substance of varying width, at times the latter is canalized and in this case the canals anastomose with those of the arterial wall; but usually canals are absent and the hyaline mass

is almost completely homogeneous. At the periphery it gradually fuses with the caseous mass. In the first stage thin, hyaline, jagged bands are seen emanating from the likewise degenerated artery in radial arrangement.

This picture, familiar from other organs, leaves no doubts about the influence of the blood circulation on the formation of canalized fibrin. It almost appears as if the hyaline had been poured, in liquid form, from the vessels into the neighboring tissue, and had coagulated there. Perhaps the presence of the caseous mass favors this diffusion.

Once or twice I was able to see tuberculous foci in the kidneys, formed by a reticulum, with its meshes enclosing round cells. The trabeculae are thickened at certain points, they become hyaline, the cells disappear and diffuse aggregates of canalized fibrin are thus formed. Arteries with degenerated walls were also found.

Since I examined a large number of miliary as well as conglomerated and caseous tubercles of the kidney, I also found hyaline casts in the uriniferous tubules in the majority of cases of renal tuberculosis. They have the same optical properties as the hyaline substance, and the question suggests itself whether both may be caused by the same degeneration, e.g. by hyaline degeneration of desqumated epithelia. One must remember, however, that casts are found in all parts of the organ and not in greater numbers near tubercles. I have found none in the tubercles proper. These casts differ from canalized fibrin primarily by their resistance to stains. When the canalized fibrin is already intensely colored, the casts have only taken on a weak coloration. More positive proof is necessary before they can be classed with the hyaline substance.

I deem it probable that the glomeruli could also be affected by hyaline degeneration, which would not be surprising considering its predilection for vessels. I found objects with the form of glomeruli, only slightly larger, consisting of a shiny mass which divided into four sections similar to the lobules of the glomerulus. They are permeated by a large number of irregular fissures in which round or oblong cells or free nuclei are found. Cells are also deposited between sections. Here and there a membrance is seen at the object's periphery, possibly the capsule of the glomerulus.

In one case of renal tuberculosis complicated by nephritis (predominantly fibrous thickening of the capsule and shrinking of glomeruli) I found a few glomeruli with a zone of canalized hyaline with nuclei in the canals. This crescent-shaped zone was deposited between the capsule and the vascular loops. This canalized fibrin was connected with the thickened capsule on one side, and on the other with the tissue that had replaced the glomerular capillaries.

We have seen that hyaline degeneration of the kidney shows a preference for blood vessels, aside from the casts whose nature is as yet

doubtful. In this organ, arteries of relatively large caliber are most frequently affected by degeneration.

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The lumps do not seem to be favorable for the development of hyaline; in 25 cases of pulmonary tuberculosis I have found it very rarely and invariably in a limited scope, as if accidental, never as generally developed as, for example, in the spleen (15).

Canalized fibrin usually takes the form of a narrow zone that gradually melts into the caseum and connects directly with the surrounding thickened connective tissue. It always has canals containing nuclei. I have never found it in the walls of cavities, nor on the surface of vascular stumps.

I should like to recall at this time that Peters (loc. cit.) has very rarely found hyaline in the ulcerative form of diphtheria, while the light cases showed the substance regularly and in copious quantities.

In one case of miliary tuberculosis, typical tubercles situated in the alveolar walls showed the beginning of hyaline degeneration.

A pronounced development was seen in a case of caseous pneumonia. In the apex of each lung there was a walnut-sized node of caseous appearance. Microscopic examination showed the following in the main part of this, apparently caseous mass. At some points the alveoli were filled with very large, round cells with granular protoplasm and one or more nuclei, connected by a network of fibrin and a considerable number of red blood cells. The alveolar walls were infiltrated by round cells, the capillaries were strongly hyperemic. At a certain point the picture suddenly changed; the wall and the content of the alveoli could still be differentiated, but both were completely altered. The cells had disappeared from the alveoli, in their place there was a delicate net of completely hyaline substance. In the net, somewhat bigger trabeculae could be distinguished, with thin branches emanating from their sides, dividing and anastomosing with neighboring branches. The meshes contain homogeneous pieces resembling cellular debris, but no stained nuclei. Most of them were empty. The alveolar walls were similarly changed; they consisted of thicker hyaline trabeculae which were arranged parallel to the surface of the wall. The blood vessels also showed degenerated walls, in part they still contained erythrocytes, some of which were found also in the neighboring meshes of the hyaline substance. At certain points, especially around the arteries, the trabeculae were slightly thicker and formed typical canalized fibrin. We have here the peculiar case of a tissue with normal and newly formed parts, both of which have succumbed to hyaline degeneration. This degeneration seems to replace caseation. It would be interesting to know the additional phases of this process.

Can hyaline assume added organization and create a form of scar, or is further organization impossible? Unfortunately I cannot clarify

this point. I have not been able to obtain positive clarification about the conditions regulating the finely meshed form of this tissue. It is not improbable that the fibrinous exudate plays a part in this process. The parts bordering on completely degenerated foci show a thickening of the fibrinous reticulum, while the interspersed cells gradually disappear; later only stained nuclei are seen in the meshes of the hyaline reticulum.

In this case we are dealing with desquamative pneumonia (fibrinous exudate and desquamation of epithelia). There is no trace of tubercles or giant cells. On the other hand, tubercles were present simultaneously in the pleura and spleen.

I was able to establish the same transformation of walls and alveolar contents in several other cases, although to a lesser extent. Among a large number of alveoli, containing caseum, there were one or two whose exudate showed hyaline metamorphosis in the form of a fine net, as in the preceding case, or in the form of lumps bordering on canals with nuclei. In one case the hyaline consisted of rosary-shaped trabeculae which formed a wide-mesh net. At times the alveolar wall alone was changed, while the alveoli contained finely granulated masses. In a similar case of caseous pneumonia, in which tuberculous intestinal ulcers and miliary splenic and renal tubercles were also present, no real tubercles or giant cells could be found. Most alveoli contained caseum, but some had a hyaline reticulum; here and there among the caseous foci, hyaline masses were found in the stroma. Some arteries in caseous foci revealed the same changes as those of the kidney, i.e. their wall manifested hyaline degeneration and was surrounded by a zone of hyaline substance.

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Adrenal gland. --- I have examined but a few cases of tuberculosis of this organ, presenting the common form with apparently caseous nodes of about 1 cm in diameter. The microscope reveals large, caseous foci with the tissue between them having an abundance of round cells, or else connective tissue with very few cells. At times the fibrous tissue is completely homogeneous and is traversed by canals containing nuclei and cells. The caseous masses consist of an opaque, granular substance with a few stained nuclei or cells. In the center there are round or oval foci interspersed with net-like hyaline. There are no nuclei, but a giant cell is sometimes found in the center, without nuclei, its edge fusing with the hyaline mass.

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Concerning testicular tuberculosis, Prof. Langhans informs me that he has only seen weak signs of fibrinous degeneration in this organ.

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Serous membranes. --- Among 10 cases of tubercular inflammation of this type of tissue I have seen degeneration twice, including a case of pericarditis. The major portion of the inflammatory new growth consisted of somewhat oblong cells connected by a thin connective tissue reticulum. In the midst of this tissue, at certain intervals, there were miliary tubercles with epithelioid and giant cells. Their center often revealed canalized fibrin. At other points the hyaline mass had replaced the whole tissue to a great extent; it had the form of a network, as in caseous pneumonia, with empty meshes or an occasional nucleus contained therein. There were a few scattered giant cells with well-preserved nuclei. The second case was one of tuberculous peritonitis. Degeneration was very weakly represented.

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Brain. --- In two cases of solitary tubercles, degeneration was found to be similar. The sectional surface showed large, caseous aggregations, with a tissue of rather diverse composition between them. For the most part it consisted of round cells which were deposited in the meshes of a thin connective tissue network. At certain points they were enlarged, some of them taking on polyhedral forms and thus turned into epithelioid cells, frequently with several nuclei. These cells formed wide avenues among round cells. In other places they became oblong, almost fusiform, and again the intercellular connective tissue was found to be highly developed, with large, fusiform cells. In all of these various forms of tissue, giant cells were quite well represented. Sometimes they were isolated, at times surrounded by epithelioid cells and forming a nodule. There was little fibrin at these places, primarily in the form of round foci resembling tubercles. It had no well-defined canals, contained no nuclei, but seemed to consist of small hyaline clods.

The central caseous masses consist primarily of granulated nuclei with distinct border contours. Some of them are strongly stained. Between them there is granular detritus. In the center of the caseous parts there were a few small vessels with hyaline walls and a homogeneous, shiny content which stained particularly well with carmine. Hyaline features appear toward the periphery of the caseum, forming a wide-mesh network; the meshes contain either a granular mass or stained or colorless nuclei, even whole cells are found on the periphery. The hyaline net fuses directly with the connective tissue reticulum found between the round cells. Only the connective tissue seems to be affected by hyaline degeneration, since the cells disintegrate to granular detritus which remains caught in the meshes of the hyaline net; the latter also succumbs to molecular division toward the caseous center.

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Considering the close resemblance between tubercle and gumma in their composition as well as in their future course, i.e. their trend to caseation, the presence of hyaline degeneration in gummata could be expected. I have examined 3 cases of syphilitic tumors and indeed found hyaline degeneration in two.

First case. --- Here, hyaline degeneration is found in miliary gummata of the spleen; I could repeat the description of this organ's tubercles, since the picture was completely identical. The gummata had the same form, consisted of the same elements, and hyaline degeneration was present in the same manner. Nothing differentiated the two types of tumors, except that a considerable number of gummata had changed almost completely into small cavities containing a substance resembling pus, which never happens in the case of tubercles. In additon, amyloid degeneration was strongly represented, so that the differences between amyloid and hyaline could be studied. Occasionally, amyloid parts were found in the peripheral, round-cell zone of the gumma, here and there almost in touch with canalized fibrin, but they were easily differentiated by their lustre and the reaction, as already stated. I could find nothing that would substantiate a transition of one substance to the other.

As proof of the fact that a syphilitic disease was involved here and not tuberculosis, I shall list a brief extract from the autopsy record. Considerable numbers of hazelnut-sized nodes in the skin (gummata). -- Glandular swellings at the throat and the axilla. Hyperosteosis of the tibia; scarred losses of pharyngeal and vaginal substance. Gummata in the esophagus and intestine, resembling those of the skin. The same nodes in the spleen. Fibrous apical induration in the lungs, without a trace of tubercles. On the kidneys, superficial scarred depressions and a few nodules on the sectional surface. Amyloid degeneration in the spleen, liver, kidneys, adrenal glands, intestine and endocardium. The liver also contained small gummata in Glisson's sheaths, with the same composition as those of the spleen, but without hyaline degeneration.

Prof. Langhans gives me the following description of the esophageal gumma that he had examined: "The small-cell outer zone is separated from the large-cell abscess only by a fairly constant zone of 0.04 mm width, distinguishable by its strong lustre and its strong imbibition of carmine under low magnification. Under high power the difference becomes less apparent, since it consists essentially of the circumstance that the fibrous intercellular substance assumes the above properties; in this connection the fibers become wider, homogeneous, with a peculiarly rigid aspect; here and there the meshes are narrow, small, more rounded. There are places in which the tissue is completely identical with diphtheritic network. Upon addition of acetic acid this mass swells up more extensively than the surrounding connective tissue. Thus there is a similarity to canalized fibrin, but no identity with it, as the meshes still contain cells and not only nuclei, in places even rather large cells, particularly in the direction of the center."

The second case was a syphilitic tumor of the lumbar enlargement and the conus medullaris of the spinal cord. As an additional symptom of syphilis, there was ostitis of the sternum, a light form of lobulated liver, swelling of the inguinal glands. The lungs were normal. There was amyloid degeneration as in the previous case.

The gumma of the spinal cord consisted primarily of a caseous mass, a turbid, finely granular substance with a moderate number of fat granules. In places there were aggregations of epithelioid cells. Hyaline degeneration is found in the same form as in the cerebral tubercles described above. It is seen on the periphery of the caseous aggregates in the form of a net with rather thick trabeculae and wide meshes. The latter contain granular detritus or glistening, homogeneous, strongly stained bodies having the shape and size of epithelioid cells. The change also affects the smaller vessels in the caseous center. Their wall is homogeneous, their contents strongly reflective and stained. There is no trace of giant cells.

The third case concerns a large caseous focus in the spleen, surrounded by scar tissue. I was unable to discover canalized fibrin.

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We have seen that canalized fibrin frequently appears in conjunction with caseum, and that it is usually located on the latter's periphery. We must conclude that fibrinous degeneration takes place first, that it is replaced by caseation, that the former is capable of changing into caseum. Indeed, I have seen this direct transition in fibrous tubercles of the spleen. The center was occupied by a turbid mass. On the border between caseum and fibrin the hyaline bands become finely granulated and opaque, without changing their form. The contours disappeared toward the center and the result was a uniform granular mass. In this case the caseum is formed by a simple molecular disintegration of hyaline.

However, in the majority of cases the transition seems to be somewhat more complicated, making it possible that different modifications of caseation are to be differentiated.

Heretofore it was usually sufficient to consider the caseous masses as aggregations of shapeless lumps, mixed with variable amounts of fat (Arnold, 16). Schueppel (17) interprets caseous degeneration as a partial fatty degeneration of all components of the tubercle; further, as shrinking of the cells due to dehydration. This ought to be the most prevalent opinion at this time, with an added reference to anemia as a special cause of the condition.

This opinion concerning simple dehydration of the tubercular elements is contradicted by the easily observable fact that the caseous parts usually bulge out above the sectional surface, which would be quite inconceivable if only a resorption of the fluid and contraction of the cells were involved. It is also quite easy to establish, by means of finely lacerated preparations, that the caseum does not consist only of amorphous elements, but that the major portion is formed by nuclei. They are rather small, round or usually oval, and not jagged (as contracted), as one would expect according to prevailing opinion; they have very distinct contours, but their substance is usually finely granular. Despite the fact that they refuse to absorb stains, their nature is unmistakable. Finely granular masses are commonly found

between nuclei, but only in small amounts, so that the whole caseum indeed seems to consist almost entirely of nuclei. This picture is most constant in caseous lungs. I have established also that upon calcification of this caseum, it is precisely these nuclei that are impregnated with calcium salts. Thus a very small grain of calcium is occasionally seen in the center of a nucleus, or a larger number more toward the periphery, or the calcium takes up the major part of the nucleus; a shiny sphere is then seen, still surrounded by a thin zone of non-calcified, light nucleic substance. Or else calcium spherules are seen next to non-calcified nuclei, completely identical in form and size. I cannot, therefore, agree with Weigert (18) when he interprets caseation as coagulational necrosis and considers nucleic atrophy its main characteristic.

Schueppel approaches this description more closely when he states that nuclei maintain themselves longer than protoplasm.

Since the nuclei are very compact, closely pressed together, it must be conceded that they are far more numerous than nuclei found at this spot at some earlier stage, be it in canalized fibrin or in the fully developed tubercle prior to the commencement of degeneration.

Only two hypotheses could explain this peculiar fact: Either the nuclei multiply extraordinarily at the moment of caseation, or they have infiltrated from without. Multiplication must be very considerable, since relatively few nuclei are found in canalized fibrin.

I cannot decide which hypothesis is correct. The fact that nuclei are found in the peripheral parts of the caseum, in the proximity of canalized fibrin which can be stained, could support either hypothesis. One observation pointed out by Prof. Langhans seems to favor infiltration. He found the lungs of a miner who had died of chronic tuberculosis to be permeated by groups of small tubercles which bordered on callous tissue with black pigment; the tissue had a knobby surface, each knob being slightly larger than the peripheral tubercles. The peripheral nodules had the composition of tubercles and the central, black masses showed the same picture, with the exception that numerous granules of pigment were found in the canals of the fibrin which surrounded the black center. As revealed by lacerated preparations, the center consisted solely of nuclei and black pigment; the black induration apparently composed of connective tissue thus turned out to be caseum with strong infiltration of coal dust. This also explained the slightly brittle state of these parts, as already noted during section. Additional disintegration naturally would lead to massive admixture of this coal to the sputum. Apparently the pigment had migrated to the tubercle's center, and this by way of the fibrin's canals. At any rate, this shows that a liquid stream had flowed here from the vasculated periphery to the center, and no one would doubt that this route could also be used by contractile elements (white blood cells).

Evidently there still exist problems whose definitive solution is still outstanding, which might lead us to the opinion that caseation is not just a simple, passive process, as universally accepted today.

Let us briefly summarize the results of our investigations:

Hyaline or fibrinous degeneration is rather frequently found in tubercles; it may occur in tubercles of all organs, but prefers certain organs (spleen, lymph glands, liver), therefore both organs afflicted by cavity formation and those not affected by ulcerous deterioration. It seems to be connected more often with the latter; at least it is rare in the lungs and entirely absent from the walls of cavities. It is a preliminary stage of caseous degeneration. ( )

Concerning its genesis, I feel certain that it is formed from the reticulum of the tubercle's peripheral zone as well as from splenic and lymph-glandular tissue; its trabeculae thicken, become homogeneous, lustrous, the meshes are compressed to canals which show nuclei as the last residue of cells.

Furthermore, it replaces epithelioid and giant cells, the former seem to change directly to homogeneous, anucleated clods. The action of giant cells remains unknown; they doubtless take part in the formation of fibrin, judging by the peculiar distribution of their nuclei.

There is a stream of fluid in the canals, moving from the tubercle's periphery toward the center; particles of coal dust enter by this passage.

Quite frequently the wall of blood vessels is changed to fibrin. During caseation the fibrin disintegrates directly to a finely granular mass or is replaced by very numerous nuclei (either descending from the nuclei in the canals or otherwise immigrated).

Explanation of the pictures.
(Table VIII, Fig. 1-3 (Zeiss E, lens IV))

Fig. 1. Picture of canalized fibrin from a splenic tubercle; slightly thicker section. The network of canals is visible, some of them are cut cross-wise. Rod-like nuclei in the canals.

Fig. 2. A very thin section; the net-like structure of the fibrin (a) is apparent. At (b) there is a giant cell, its jagged edge interlocking with fibrin. At (c) transition of fibrin to the splenic reticulum.

Fig. 3. Cross section through an arterial wall (spleen).
(a) Hypertrophic intima. (b) Media transformed to canalized fibrin.
(c) Canalized fibrin surrounding the artery.

NOTES.

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